Preoperative clonidine blunts hyperadrenergic and hyperdynamic responses to prolonged tourniquet pressure during general anesthesia

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Abstract: Although the mechanism of tourniquet-induced hypertension is still unclear, plasma norepinephrine concentrations continuously increase in parallel to arterial blood pressure during tourniquet inflation. Clonidine attenuates hyperadrenergic and hyperdynamic responses. We investigated the effects of clonidine on prolonged tourniquet inflation. Twenty-nine patients scheduled for elective orthopedic surgery were randomly assigned to receive IV clonidine (3 microg/kg; n = 14) or placebo (n = 15) before tourniquet inflation of the lower limbs under general anesthesia in a double-blinded manner. Arterial blood pressure, heart rate, epinephrine, and norepinephrine plasma concentrations were measured before tourniquet inflation, 60 min after tourniquet inflation, just before tourniquet deflation, and 20 min after tourniquet deflation. Mean arterial blood pressure and norepinephrine plasma-concentrations were significantly lower in the Clonidine group compared with Control after 60 min tourniquet inflation (P = 0.016; P = 0.006). Immediately before deflation of the tourniquet, the difference for mean arterial pressure between groups was even more pronounced (P = 0.005). Twenty minutes after deflation mean arterial blood pressure in the Control group was still increased and significantly higher compared with the Clonidine group (P = 0.002). In conclusion, preoperative IV clonidine blunts hyperadrenergic and hyperdynamic responses resulting from prolonged tourniquet inflation under general anesthesia in ASA class I–II patients. IMPLICATIONS: Tourniquet inflation is associated with a continuous increase in arterial blood pressure and sympathetic outflow. This study shows that IV clonidine effectively blunts increases of both arterial blood pressure and plasma norepinephrine concentrations.

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Preoperative Clonidine Blunts Hyperadrenergic and Hyperdynamic Responses to Prolonged Tourniquet Pressure During General Anesthesia

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Although the mechanism of tourniquet-induced hypertension is still unclear, plasma norepinephrine concentrations continuously increase in parallel to arterial blood pressure during tourniquet inflation. Clonidine attenuates hyperadrenergic and hyperdynamic responses. We investigated the effects of clonidine on prolonged tourniquet inflation. Twenty-nine patients scheduled for elective orthopedic surgery were randomly assigned to receive IV clonidine (3 μg/kg; n = 14) or placebo (n = 15) before tourniquet inflation of the lower limbs under general anesthesia in a double-blinded manner. Arterial blood pressure, heart rate, epinephrine, and norepinephrine plasma concentrations were measured before tourniquet inflation, 60 min after tourniquet inflation, just before tourniquet deflation, and 20 min after tourniquet deflation. Mean arterial blood pressure and norepinephrine plasma-concentrations were significantly lower in the Clonidine group compared with Control after 60 min tourniquet inflation (P = 0.016; P = 0.006). Immediately before deflation of the tourniquet, the difference for mean arterial pressure between groups was even more pronounced (P = 0.005). Twenty minutes after deflation mean arterial blood pressure in the Control group was still increased and significantly higher compared with the Clonidine group (P = 0.002). In conclusion, preoperative IV clonidine blunts hyperadrenergic and hyperdynamic responses resulting from prolonged tourniquet inflation under general anesthesia in ASA class I–II patients.

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Tourniquet inflation has become a standard procedure in orthopedic and plastic surgery of upper and lower limbs. Bleeding is significantly reduced and the surgical conditions for preparation are excellent using this technique. However, tourniquet inflation is also associated with severe pain, augmented sympathetic outflow, and a continuous increase in systemic arterial blood pressure (1–5). The onset of tourniquet hypertension is delayed and its treatment is difficult and often ineffective, even with increased doses of anesthetics and antihypertensive drugs (6). Although the mechanism of tourniquet hypertension is unknown, the autonomic nervous system is involved and plasma-catecholamine concentrations are increased (3,7). Clonidine attenuates hyperadrenergic responses and therefore may be of therapeutic and prophylactic value for tourniquet hypertension (8,9). The purpose of this study was to investigate the effects of preoperative IV clonidine on arterial blood pressure and plasma-catecholamine concentrations during prolonged tourniquet inflation of the lower limbs under general anesthesia.

Methods

The study was randomized, double-blinded and placebo-controlled. After obtaining Ethics Committee approval and written informed consent, 40 ASA class I and II patients were enrolled. All patients were randomly assigned to either receive IV clonidine or plain saline infusion. Inclusion criteria were ASA class I–II and elective orthopedic surgery with tourniquet inflation of the lower limbs. Exclusion criteria were as follows: history of cardiac arrhythmias or cardiovascular disease, including hypertension; atrioventricular block; congestive heart failure; cardiac medication; expected tourniquet time shorter than 60 min or longer

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than 150 min. After enrollment 11 patients with a tourniquet time shorter than 60 min or longer than 150 min were excluded.

All patients received oral midazolam 7.5 mg 45–60 min before induction of anesthesia. Patients in the IV Clonidine group ($n = 14$) received 3 μg/kg clonidine in a 10-min saline infusion (100 mL) immediately before induction of anesthesia. Patients in the Control group ($n = 15$) received plain saline infusion (100 mL). The infusions were prepared and blinded in advance by an anesthesia nurse according to the random list. Anesthesia was induced with fentanyl 1–2 μg/kg and thiopental 5 mg/kg. Pancuronium or atracurium was used for muscle paralysis. Mean arterial blood pressure before induction of anesthesia was measured noninvasively. After anesthesia induction a 14-gauge cannula was inserted in a large cubital vein for taking blood samples, and a radial artery catheter was inserted for invasive blood pressure measurements. Anesthesia was maintained with isoflurane and N_2O in 30% oxygen. Muscle paralysis was maintained with pancuronium or atracurium. Tidal volume was adjusted to keep the end-tidal CO_2-concentration between 4.5% and 5%. If mean arterial blood pressure exceeded 130 mm Hg despite increased doses of isoflurane and fentanyl up to an intraoperative total dose of 3 μg/kg an additional bolus of clonidine 30 μg would be given.

All variables (mean arterial blood pressure, heart rate, norepinephrine, epinephrine, end-tidal CO_2-concentration, and end-tidal isoflurane concentration) were measured at the following three time points:

A. Baseline measurement under general anesthesia *before* surgery *and* tourniquet inflation.
B. During surgery at 60 min tourniquet time.
C. Immediately before tourniquet deflation.

To determine plasma-catecholamine concentrations the 10-mL EDTA tubes were placed on ice immediately after venous sampling, then centrifuged promptly at +4°C to separate the plasma, and finally stored at −70°C until analyzed with high-performance liquid chromatography (10). Monitoring consisted of electrocardiogram, measurement of radial artery blood pressure, end-tidal CO_2-concentration, end-tidal isoflurane concentration, and oxygen saturation, obtained by pulse oximetry (VICOM-SM SMU 612, PPG-Hellige, Freiburg, Germany).

Randomization and statistical analysis were made using StatView for Windows v. 5.0 (SAS Institute Inc., Cary, NC) and SPSS 10.0 for Windows (SPSS Inc., Chicago, IL). Data are presented as mean ± SD. The distribution of female to male patients was compared using Fisher's exact test. Continuous data were compared using the Mann-Whitney *U*-test. $P < 0.05$ was considered statistically significant. Bonferroni correction was made for multiple comparisons at relevant time points (B and C). To assess whether the effect of clonidine found in the univariate analysis was an independent one or might have been mediated by demographic or baseline values, repeated-measures analysis of variance with within-factor time (points B and C), between-factor group (clonidine versus control), and one covariate were performed. For the analysis of a possible effect of gender, a repeated-measures analysis of variance with two between factors was performed. For these analyses, norepinephrine plasma-concentrations were log-transformed to reach an approximately normal distribution.

Results

Both groups of patients were similar with regard to demographic characteristics and tourniquet time (Table 1).

The values for all variables (mean arterial blood pressure, heart rate, norepinephrine, epinephrine, and end-tidal isoflurane concentration) were similar at time point A (baseline measurements) in both groups (Fig. 1). Mean arterial blood pressure and norepinephrine plasma concentrations were significantly smaller in the Clonidine group compared with Control after 60 min tourniquet inflation ($P = 0.016$; $P = 0.006$; Fig. 1, B) and immediately before deflation ($P = 0.005$; $P = 0.016$; Fig. 1, C). Heart rate, epinephrine plasma concentration, and end-tidal isoflurane concentration were similar in both groups at time points B and C.

Under general anesthesia 20 min after deflation of the tourniquet mean arterial blood pressure in the Control group was still increased and significantly higher compared with the Clonidine group (84 ± 11 versus 71 ± 8 mm Hg; $P = 0.002$).

Multivariate Analysis

For all repeated-measures analysis of variance performed, the effect of clonidine remained significant independently of covariate analyzed ($P < 0.01$ for mean arterial blood pressure and $P < 0.023$ for norepinephrine plasma-concentrations). The baseline value of norepinephrine plasma concentration had a significant effect on values at time points B and C ($P = 0.02$ for group, $P = 0.045$ for baseline value). No other effects were significant. Furthermore, neither preanesthetic values nor baseline values of mean arterial blood pressure had any influence on values of mean arterial blood pressure at time points B and C.

Intra- and postoperatively, maximum mean arterial blood pressure was 109 mm Hg. No serious cardiovascular events occurred and neither inotropic nor chronotropic medication had to be administered.

Discussion

Perioperative hypertension may be associated with serious cardiac complications (11–13). Furthermore,

Table 1. Demographic Data, Tourniquet Time and Preanesthetic Blood Pressure

	Clonidine (n = 14)	Control (n = 15)
Age (yr)	32 ± 12	35 ± 11
Sex (m/f)	9/5	9/6
Weight (kg)	77 ± 13	75 ± 15
Height (m)	1.77 ± 0.09	1.71 ± 0.08
Tourniquet time (min)	91 ± 25	93 ± 22
Mean arterial blood pressure (mm Hg)	95 ± 6	91 ± 9

Values are mean ± SD. Mean arterial blood pressure is before induction of anesthesia, measured noninvasively. There were no significant differences between groups.

the level of hypertension is correlated with the occurrence of postoperative silent myocardial ischemia (13). The intraoperative hypertension induced by prolonged tourniquet inflation of the lower limbs is often unresponsive to increased doses of anesthetics and antihypertensive drugs (6). The results of this study clearly indicate that preoperative IV clonidine blunts both tourniquet hypertension and increases in norepinephrine plasma concentrations. These variables were significantly decreased in the Clonidine group after 60 minutes of tourniquet inflation and before deflation of the tourniquet. After deflation mean arterial blood pressure in the Control group was still significantly higher.

The precise mechanism of tourniquet hypertension is unknown. However, a few hypotheses have been discussed. Satsumae et al. (14) recently argued that tourniquet hypertension might be related to *N*-methyl-D-aspartic acid (NMDA) receptor activation by peripheral noxious stimuli from the extremities and that ketamine, as NMDA receptor antagonist, might attenuate tourniquet hypertension. They showed that systolic arterial blood pressure was significantly reduced during tourniquet inflation in the two ketamine-treated groups compared with the control group. Although the study results seem to support their hypothesis, tourniquet time was significantly longer in the control group (101 min versus 86 min; $P < 0.02$). In fact, the tourniquet-induced increase in arterial blood pressure is continuous (15); this has been confirmed again in our study (Fig. 1). Systolic arterial pressure possibly would have been lower in the control group if tourniquet time was as short as in the ketamine groups. Plasma catecholamines were not measured. The effect of ketamine on increased sympathetic outflow might have been of interest in this study setting.

Heropoulos et al. (7) evaluated the effects of enalaprilat, an angiotensin-converting enzyme inhibitor, on hemodynamic and hormonal responses to prolonged tourniquet inflation. They could not demonstrate a blunting effect on increases in arterial blood pressure or norepinephrine plasma concentrations.

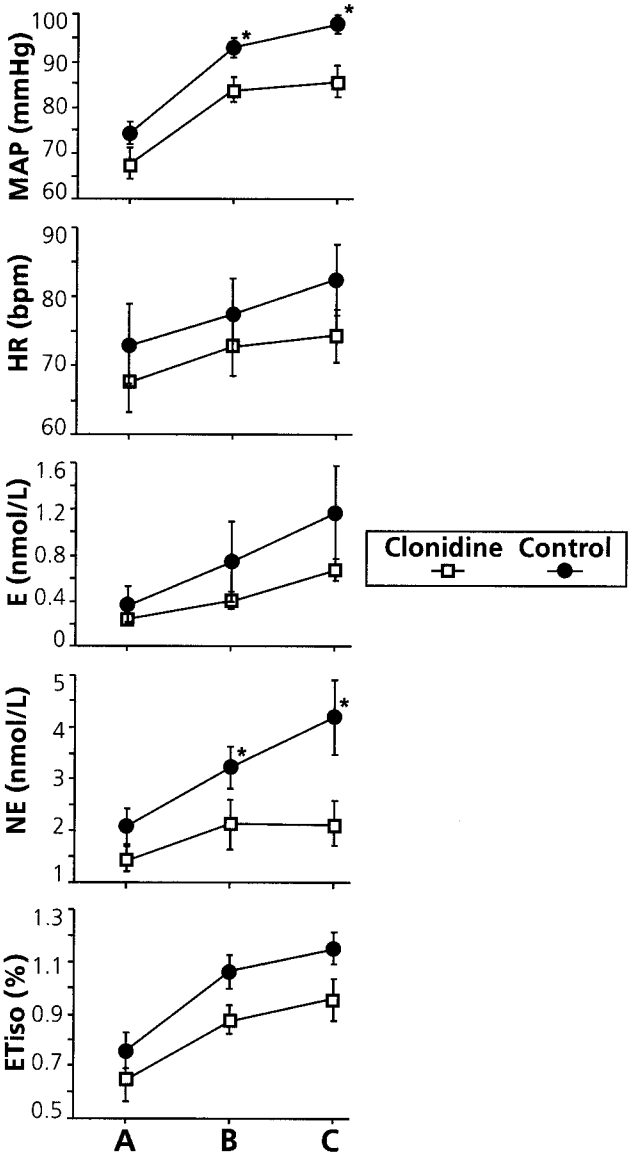

Figure 1. All variables at the following time points: A, preoperative baseline measurement after infusion of saline or clonidine, after induction of anesthesia and before tourniquet inflation; B, 60 min after tourniquet inflation; and C, just before tourniquet deflation. MAP = mean arterial blood pressure; HR = heart rate; E = epinephrine plasma concentration; NE = norepinephrine plasma concentration; Etiso = end-tidal isoflurane concentration. Values are expressed as mean ± SD. *significant differences ($P < 0.017$) in variables between Clonidine and Control after Bonferroni correction.

Another hypothesis on tourniquet-induced hypertension regards the correlation with autonomic nervous system changes, which was also the working hypothesis of this study. On the basis of power spectral heart rate analysis, Tetzlaff et al. (3) showed that tourniquet hypertension is correlated with the activation of the sympathetic nervous system. Heropoulos et al. (7) demonstrated that tourniquet hypertension is associated with an increase in plasma catecholamines.

Clonidine reduces the presynaptic norepinephrine release, decreases the "set point" around which blood pressure is regulated, and has a substantial analgesic and sedative action (16,17). Clonidine blunts responses to various qualities and quantities of perioperative stress (8,9,16,17); this has also become a subject of molecular research (18,19). In awake patients the addition of clonidine to the local anesthetic solution in IV regional anesthesia prevents tourniquet pain (20,21) However, this study provides new evidence that preoperative IV clonidine blunts both the increase in sympathetic outflow and the arterial hypertension induced by tourniquet inflation under general anesthesia.

We measured the end-tidal isoflurane concentration to compare the level of sedation between the groups. Although the end-tidal isoflurane concentrations were similar in both groups at all time points (Fig. 1) this may be a limitation of our study design. Bispectral index (BIS) or auditory evoked potential index appear to give more information. However, the sensitivity and specificity of these methods are not 100 percent (22–24) and BIS does not consistently correlate with the level of sedation, especially during isoflurane anesthesia (25). In Figure 1 it is noticeable that the mean values of end-tidal isoflurane concentration were lower in the Clonidine Treated group throughout the whole study period, although the difference did not reach statistical significance. This may be explained by the finding that clonidine, aside from or perhaps by its effects on arterial blood pressure or norepinephrine plasma concentrations, reduces isoflurane requirements (26).

In summary, preoperative IV clonidine significantly blunts hyperadrenergic and hyperdynamic responses to prolonged tourniquet inflation of the lower limbs under general anesthesia in ASA class I and II patients. On the basis of the results of this study, further investigations are needed to show whether perioperative outcome in patients with arterial hypertension or cardiovascular disease is improved by clonidine treatment.

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